Acid-Base, Electrolytes, and Renal Failure

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Metabolic acidosis is a well-recognized component of chronic renal failure (CRF). Metabolic acidosis in renal failure results primarily from the limited ability of failing kidneys to excrete hydrogen ions and regenerate bicarbonate. Normal acid-base balance is maintained by a combination of tubular reabsorption of filtered bicarbonate and excretion of hydrogen ions with ammonia and urinary buffers, primarily HPO_4^{2-} (termed titratable acidity). Renal excretion of hydrogen ions effectively regenerates bicarbonate lost via the gastrointestinal or urinary tracts or through respiratory buffering of metabolic acids. As the quantity of functioning renal mass declines in CRF, hydrogen ion excretion is maintained largely by increasing the quantity of ammonium excreted by surviving nephrons. However, at some level of renal dysfunction, the capacity to further increase renal ammoniagenesis is lost and metabolic acidosis ensues. It is assumed that the fall in total ammonium excretion that occurs in advanced renal failure results from the limited number of functioning nephrons. Decreased medullary recycling of ammonia due to structural renal damage may also contribute to impaired ammonium excretion.

In a retrospective case series of cats with renal failure, approximately 80% had metabolic acidosis based on decreased venous blood pH values and bicarbonate concentrations.[1] In contrast, acidosis appears to occur less consistently in dogs with chronic renal failure. There is some evidence that feline kidneys may respond differently to metabolic acidosis as compared with other mammalian species studied. One investigator has shown that acidosis fails to increase the rate of production of ammonia in cultured feline proximal tubular cells.[2] Whether cats are at increased risk for developing metabolic acidosis because of this limitation is unknown, but the unexpectedly high incidence of acidosis in cats with CRF would be consistent with this suggestion.

Although species-related differences in renal acid excretion may contribute to this apparent difference, it is likely that the high incidence of uremic acidosis in cats relates, at least in part, to the acidifying nature of many cat foods. It has been speculated that routine use of acidifying diets may contribute to the relatively high incidence of chronic renal failure observed in cats over the past decade. Further, uremic acidosis may contribute to the chronic wasting typical of renal failure.

Clinical Manifestations of Acidosis

Chronic metabolic acidosis promotes a variety of adverse clinical effects including anorexia, nausea, vomiting, lethargy, weakness, muscle wasting, and weight loss. Alkalization therapy appears to be of value in reversing these signs. In addition, chronic mineral acid feeding to dogs has been shown to increase urinary calcium excretion and progressive bone demineralization, the magnitude of which de-

pends on age and dietary calcium levels. Studies on the effects of dietary acidification in cats have revealed that chronic metabolic acidosis can cause negative calcium balance and bone demineralization or negative potassium balance, which may in turn promote hypokalemia, renal dysfunction, and taurine depletion.[3] Severe acidemia (blood pH values below 7.20) may result in decreased cardiac output, arterial pressure, and hepatic and renal blood flows and centralization of blood volume.[4] Centralization of blood volume results from peripheral arterial vasodilatation and central venoconstriction. Decreases in central and pulmonary vascular compliance may predispose patients to pulmonary edema during fluid administration, an effect that may be particularly important in patients with acute uremic crises requiring intensive fluid therapy. Acidemia also promotes reentrant arrhythmias and a reduction in the threshold for ventricular fibrillation.

Severe acidosis may also influence carbohydrate and protein metabolism, serum potassium concentrations, and brain metabolism.[4] Acidemia can decrease tissue glucose uptake by inducing insulin resistance and inhibit anaerobic glycolysis by depressing 6-phosphofructokinase activity. Net protein breakdown may be increased by acidemia. Acidemia promotes hyperkalemia through translocation of potassium out of cells, an effect that is more prominent with nonorganic acidosis than with organic or respiratory acidosis. Severe acidemia impairs brain metabolism and volume regulation, leading to progressive obtundation and coma.

Does Acidosis Injure the Kidneys?

Metabolic acidosis has been theorized to enhance progression of renal failure by promoting renal ammoniagenesis and activation of the alternative complement pathway. Elevated renal parenchymal ammonia concentrations may be one of the common pathways whereby diverse renal insults result in similar pathologic manifestations of renal injury.[5] Renal ammoniagenesis is augmented by chronic metabolic acidosis, hypokalemia, subtotal renal ablation, feeding high-protein diets, diabetic nephropathy, and antioxidant (vitamin E or selenium) deficiency. All of these states are associated with the induction or progression of renal failure in an experimental model or clinical disease state. High tissue ammonium concentrations activate the

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third component of complement by the alternate pathway. Complement-mediated renal inflammation results in tubulointerstitial damage, which may in turn promote progression of renal disease. Preventing metabolic acidosis using sodium bicarbonate supplementation prevents the development of tubulointerstitial lesions in rats with induced CRF.

Increased ammoniagenesis may also contribute to progressive renal injury by other mechanisms. High ammonia levels may promote growth of renal cells in culture; renal hypertrophy is yet another central mechanism that appears to mediate progression of CRF in many disease states. Another theory states that increased urine osmolality (reflecting increased workload of interstitium to generate gradients for excretion) induces renal hypertrophy and progression of CRF. Either acidosis or a high-protein diet would augment ammonium production, contributing added solutes and requiring increased urine concentration.

However, more recent studies in rats have questioned the role of acidemia and enhanced renal ammoniagenesis.[6] Longer-term studies have suggested that the effects noted by Nath et al.[5] may have been transient or short-term, possibly related to the timing of therapeutic intervention in the previous study. These researchers concluded that metabolic acidosis neither causes nor exacerbates chronic renal injury. Further, treatment of uremic acidosis was deemed unlikely to influence disease progression in patients with chronic renal failure.

Acidosis and Protein Metabolism

Chronic acidosis may promote protein malnutrition in patients with CRF. Although poorly understood, the multiple causes of protein malnutrition appear to include poor appetite, excessive dietary protein restriction, hormonal imbalances, abnormal energy metabolism, and metabolic acidosis. Protein catabolism is increased in patients with acidosis to provide a source of nitrogen for hepatic glutamine synthesis, glutamine being the substrate for renal ammoniagenesis.[7] Evidence from studies of rat muscle suggests that uremia directly impairs insulin-stimulated protein synthesis independent of metabolic acidosis. On the other hand, protein degradation is stimulated by metabolic acidosis, even in nonuremic states. The combined effects of reduced protein synthesis due to uremia and accelerated proteolysis

due to acidosis promote elevations in blood urea nitrogen, increased nitrogen excretion, and negative nitrogen balance typical of uremic acidosis. Altered branched chain amino acid metabolism appears to be involved. Chronic metabolic acidosis increases the activity of muscle branched chain keto acid dehydrogenase, the rate-limiting enzyme in branched chain amino acid catabolism. This is important in that branched chain amino acids are rate limiting in protein synthesis and play a role in regulation of protein turnover. Alkalization therapy effectively reverses acidosis-associated protein breakdown. Although glucocorticoids appear to be essential for acidosis-induced protein catabolism, this response can be blocked in uremic animals by correcting acidosis despite persistent increases in glucocorticoid levels. There is speculation that changes in intracellular pH accompanying acidosis lead to alterations in gene transcription, which increase the activity of the cytosolic ATP- and ubiquitin-dependent protein degradation pathway. Severe chronic metabolic acidosis has the potential to induce a cycle of progressive protein malnutrition and metabolic acidosis. Excessive protein catabolism may lead to protein malnutrition despite adequate dietary intake. This process may then accelerate breakdown of endogenous cationic and sulfur-containing amino acids, thus promoting further acidosis.

Acidosis poses a particularly vexing problem for CRF patients consuming protein-restricted diets. Dietary protein requirements appear to be similar for normal humans and humans with CRF unless uremic acidosis is present. When acid-base status is normal, adaptive reductions in skeletal muscle protein degradation protect patients consuming low-protein diets from losses in lean body mass. In rats and humans these adaptive responses may be overridden even by mild acidosis. Thus acidosis may limit the ability of patients to adapt to dietary protein restriction. These findings have not yet been confirmed in dogs and cats.

Recent studies have suggested that correcting even relatively mild acidosis in humans with renal failure receiving chronic ambulatory peritoneal dialysis may translate into improved nutrition and, most importantly, reduced morbidity.[8] Reduced morbidity in these patients meant fewer admissions to hospital and shorter hospital stays.

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Treatment of Metabolic Acidosis

Alkalization therapy designed to correct metabolic acidosis is an important part of the overall management of patients with CRF. Potential benefits of alkalization therapy in patients with chronic renal failure include:

- Improving signs of anorexia, lethargy, nausea, vomiting, muscle weakness, and weight loss, which may be caused by uremic acidosis
- Preventing the catabolic effects of metabolic acidosis on protein metabolism in patients with chronic renal failure, thereby promoting adaptation to dietary protein restriction
- Enhancing the patient's capacity to adapt to additional acid stress resulting from such factors as diarrhea, dehydration, or respiratory acidosis
- Limiting skeletal damage (demineralization and inhibited skeletal growth) resulting from bone buffering
- Rectifying the adverse effects of severe acidosis on the cardiovascular system (impaired myocardial contractility and enhanced venoconstriction)

Because even mildly reduced plasma bicarbonate concentrations may promote some of the adverse effects of chronic metabolic acidosis, oral alkalization therapy is indicated when serum bicarbonate concentration declines to 17 mEq/L or less (total CO_2 concentrations of 18 mEq/L or less). A word of caution is necessary regarding the use of serum total CO_2 concentrations determined on chemical autoanalyzers as a method to monitor metabolic acidosis and therapy. When blood collection tubes are not fully filled or left exposed to air while awaiting analysis, the vacuum or air above the tube can draw CO_2 out of the serum, falsely lowering CO_2 concentrations. This may result in a falsely low total CO_2 reading and an incorrect conclusion that the patient has metabolic acidosis. In addition, there may be a substantial systematic difference between blood bicarbonate concentrations determined by blood gas analysis and serum total CO_2 concentrations determined on autoanalyzers due to inherent differences in the analysis methods. Appropriate reference ranges are equipment and method specific, and therefore published ranges for therapeutic goals must be extrapolated with cau-

tion. It is possible that problems associated with clinical determination of acid-base status may have resulted in artifactually expanded reference ranges and clinician mistrust of the accuracy of total CO_2 determinations, resulting in an underappreciation of the true prevalence of metabolic acidosis in CRF.

Oral sodium bicarbonate is the most commonly used alkalinizing agent for patients with metabolic acidosis of CRF. Because the effects of gastric acid on oral sodium bicarbonate are unpredictable, the dosage should be individualized for each patient. The suggested initial dose of sodium bicarbonate is 8 to 12 mg/kg body weight given every 8 to 12 hours.

Potassium citrate is a particularly attractive alternative alkalization agent. Potassium citrate may offer the advantage, at least in cats, of allowing for the simultaneous treatment of both hypokalemia and acidosis with a single drug. When accompanied by potassium depletion or magnesium depletion, metabolic acidosis may respond poorly to alkali therapy alone. There is a risk for overalkalization, however, in that potassium doses required for adequate correction of hypokalemia may exceed the citrate dose required to correct acidosis. Starting doses of 0.3 to 0.5 mEq/kg of potassium (1 mEq potassium is equivalent to 1 mEq of bicarbonate in PolyCitra®-K [ALZA Corporation]) every 12 hours are recommended.

Regardless of the alkalinizing agent chosen, administration of several smaller doses is preferred to a single large dose in order to minimize fluctuations in blood pH. The patient's response to bicarbonate therapy should be determined by measuring blood bicarbonate or serum (plasma) total CO_2 concentrations 10 to 14 days after initiating therapy. Ideally, blood should be collected just prior to administration of the drug. The goal of therapy is to maintain blood bicarbonate (or serum total CO_2) concentrations within the normal range. Dosage should be adjusted according to changes in blood bicarbonate (or serum total CO_2) concentrations. Urine pH is often insensitive as a means of assessing the need for or response to treatment and is not routinely recommended for these purposes.

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